Silylium-Catalyzed Activation of Donor-Acceptor Strained Rings and Annulation with Indoles

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Abstract: Leveraging the unique reactivity profile of donor-acceptor aminocyclopropanes and cyclobutanes allows the preparation of complex nitrogen-substituted molecules. While most reports focus on donor-acceptor strained rings with two geminal carbonyl groups as acceptors, mono carbonyl acceptor systems, despite their synthetic relevance, have been considerably less studied. Herein we describe catalytic annulation reactions of aminocyclopropane and aminocyclobutane monoesters employing silylium catalysis to activate these less reactive donor-acceptor systems.

Keywords: Alkaloids · Cycloadditions · Donor-acceptor systems · Silylium catalysis
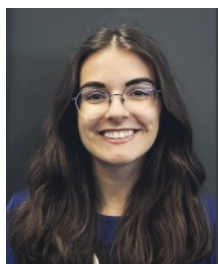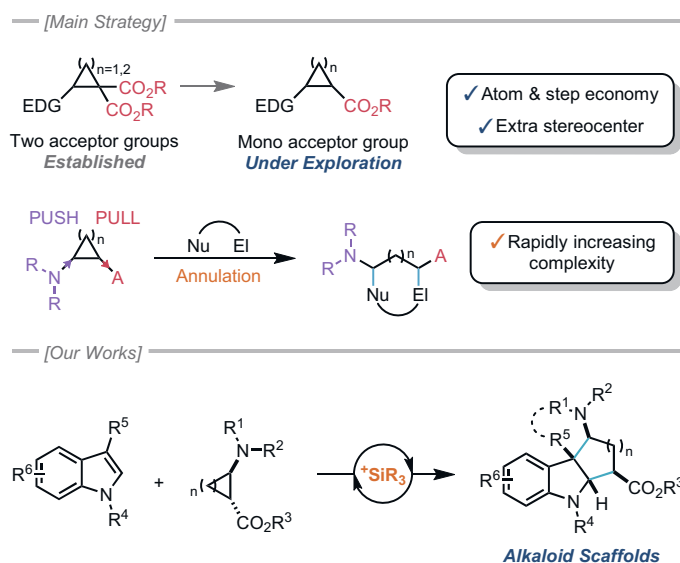
Emma G. L. Robert was born in Lyon (France). She has a BSc and MSc in chemistry and chemical engineering from CPE Lyon and an MSc in organic synthesis from the University Claude Bernard Lyon 1 (UCBL, France). In 2019, she joined the Broad Institute of MIT and Harvard (Cambridge, MA, USA) where she was working as a medicinal chemistry intern. She then joined the group of Prof. Jérôme Waser (EPFL, Switzerland) as an intern, studying decarboxylative cyclization strategy. Emma is now developing strained rings synthesis and activation using Lewis acid catalysis as a PhD student in the same group.

1. Introduction

Donor-acceptor (DA) cyclopropanes, characterized by vicinal substitution with electron-donating and electron-accepting groups, are one of the most studied strained ring motifs.[1] The bond between the donor and acceptor groups exhibits high polarization and can undergo cleavage upon appropriate activation. In the presence of an external nucleophile-electrophile moiety, the activated ring can participate in annulation reactions, leading to the formation of cyclic structures and the creation of two new bonds (Scheme 1).

Maintaining an electronic balance between the donor and the acceptor substituents is crucial for creating push-pull systems that are both reactive and bench-stable. While most reports focus on DA strained ring systems with malonyl diester groups as acceptors, typically activated by a di-coordinating Lewis acid; mono carbonyl acceptor systems have been less explored despite their synthetic importance. In particular, these systems provide an extra stereocenter and no additional decarboxylation step post-product formation is required. Yet, the limited occurrences of annulation reactions using a single acceptor group usually require a stoichiometric amount of activator and are poorly selective.[1d,2]

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Scheme 1. Donor-acceptor strained rings: activation principle and application to alkaloid synthesis.

Nitrogen-substituted cyclic structures are widespread in both natural products and synthetic bioactive compounds. Exploiting the unique reactivity profile of donor-acceptor strained rings enables the preparation of complex nitrogen-substituted molecules.[3] In this regard, the nitrogen moiety plays a dual role, crucial for both activating the strained ring and is contributing to the synthetic importance of the final products.
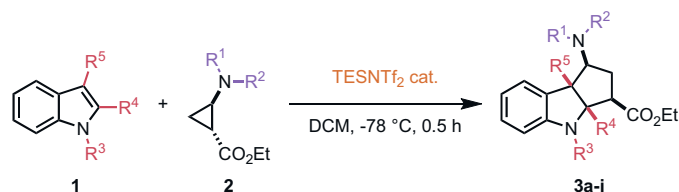
In our quest for efficiency in constructing nitrogen-substituted molecules, we started to study the reactivity of DA amino strained ring monoesters. Our investigations started with the annulation reaction between these systems and indole derivatives.[4,5] This approach effectively produces indole-fused cyclopentyl- or cyclohexyl-amines, which constitute the core structure of akuamma alkaloids such as vindolinine, pleiomutinine, akuammanicine, or strychnine.

## 2. Catalytic Activation of Aminocyclopropane Monoesters

In 2021 we published the first annulation reaction using these cyclopropane monoesters.[4] The key to success laid in employ-

ing silyl bistriflimide as a catalyst, effectively activating the less-reactive rings in a [3+2] dearomative annulation with indoles (Scheme 2). Several protecting groups were introduced on the nitrogen of the indole, such as PMB, Bn or TBS (**3a**-**3c**). Moreover, this method stands out for its ability to accommodate various substitution patterns. Indeed, substitution at both C(2) (**3d**, 94% yield, dr 75:25) and C(3) (**3e**, 84% yield, dr 71:29) of the indole were tolerated. The reaction can also be performed intramolecularly as shown with **3f** (59% yield, dr >95:5). Starting with a bicyclic cyclopropane, the tetracyclic compound **3g** (75% yield, dr 67:33) was obtained. A fully substituted center at the donor position could be accessed (**3h**, 27% yield, dr >95:5). Finally, this reaction enabled the introduction of a non-symmetrical, all-carbon quaternary center at the acceptor position (**3i**, 78% yield, dr 88:12) for the first time, which demonstrated the potential of using mono-acceptor strained rings.
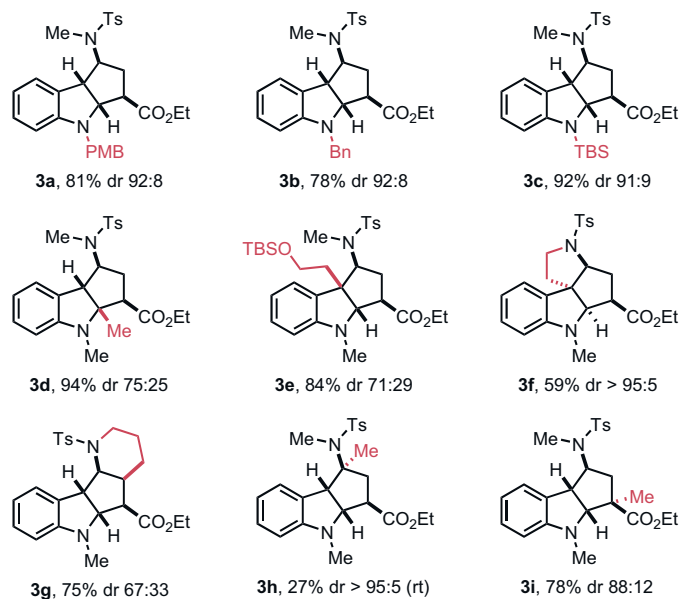

Scheme 2. Scope of the dearomative [3+2] annulation of DA-aminocyclopropane monoesters and indoles.

3. From Cyclopropanes to Cyclobutanes

Unlike their cyclopropane counterparts, donor-acceptor amino cyclobutanes have received less attention, despite sharing similar ring strain energy.[6] The first challenge lays in accessing donor-acceptor aminocyclobutane monoesters. Up until 2023, when we disclosed our last method,[5] no annulation of such strained rings preserving the nitrogen functionality had been documented.

3.1 *Synthesis of DA Aminocyclobutane Monoesters*

We found that β-aminocyclobutane monoesters could be accessed from the Michael addition of sulfonamides onto cyclobutenes (Scheme 3).[5] Starting from commercially available α-bromocylobutane esters **4**, the cyclobutene intermediates were generated *in situ* after dehydrobromination using DBU. A variety of DA aminocyclobutenes could be generated using this method in 42-83% yield (see examples: **5a–5h**).
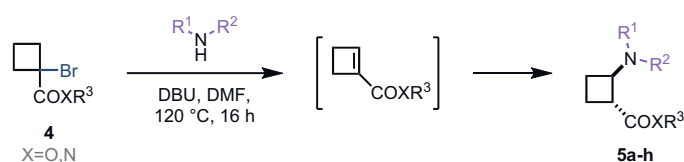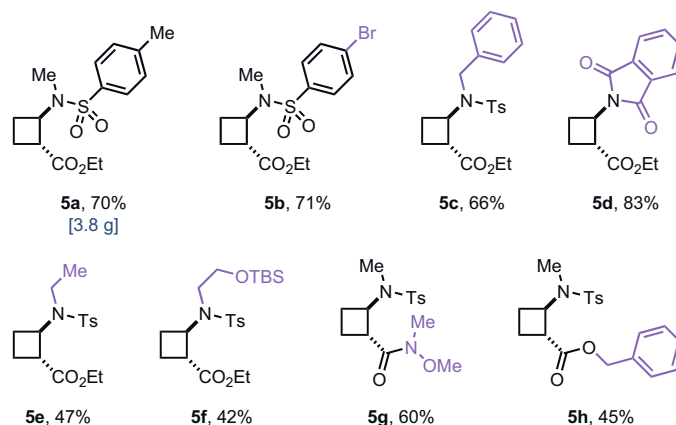

Scheme 3. Synthesis of DA amino cyclobutanes from commercially available bromo cyclobutane **4**.

3.2 *Inter- and Intra-molecular Annulation with Indoles*

After having accessed a novel library of DA cyclobutanes, we initiated investigations into catalytic [4+2] annulation reaction with indoles (Scheme 4). We found that a similar silylium catalysis strategy could be employed to activate the monoester strained rings, but a higher temperature was required (40 °C *vs* -78 °C). The reaction was performed intermolecularly to afford products **6a-f**. PMB, Bn and allyl could be used as protecting groups on the indoles (**6a-6c**). Substituents on the C(3) position of the indole were tolerated as shown for **6d** (18% yield, dr >95:5). Variations on the cyclobutane moiety were also explored (**6e-6f**).
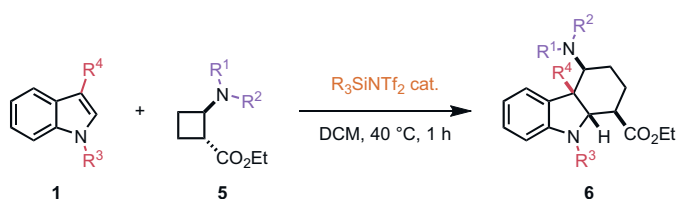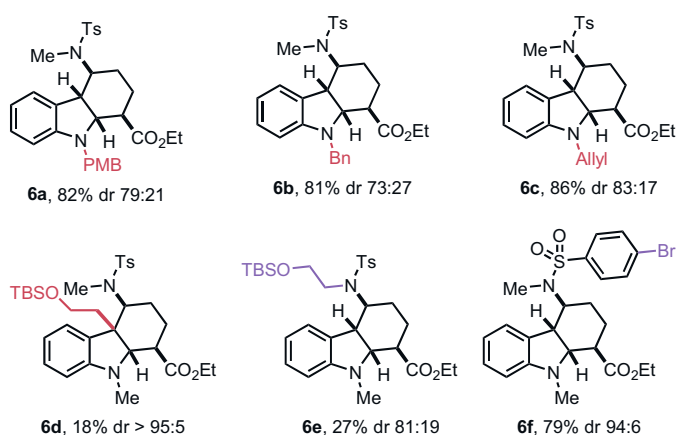

Scheme 4. Scope of inter-molecular [4+2] annulation of DA-aminocyclobutane monoesters and indoles.

We then studied the *intra*-molecular [4+2] annulation (Scheme 5). Interestingly, varying the reaction temperature resulted in a complete switch of the reaction outcome. At 40 °C, the major isomer **8** (quant. yield, 27:73 isomer ratio) exhibited the characteristic core structure of malagasy alkaloids, while at –50 °C, the main isomer **9** (67% yield, 95:5 isomer ratio) displayed the
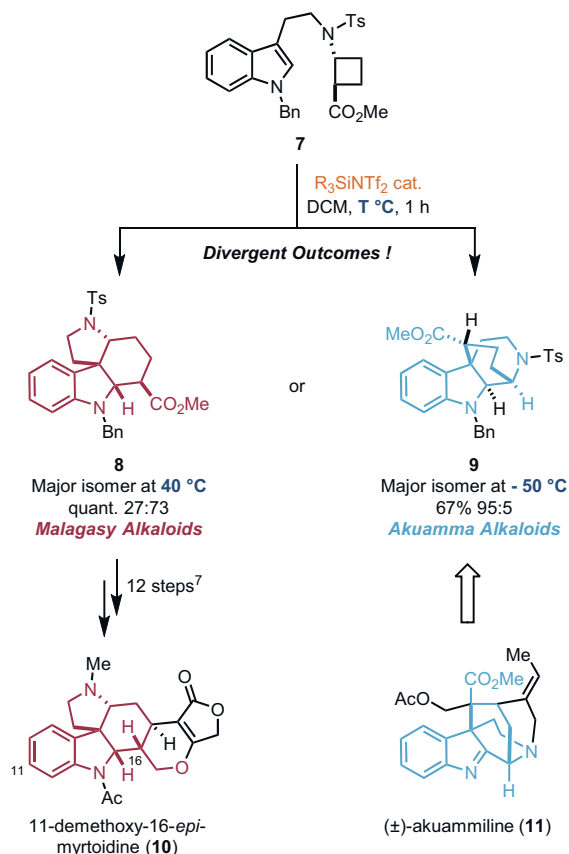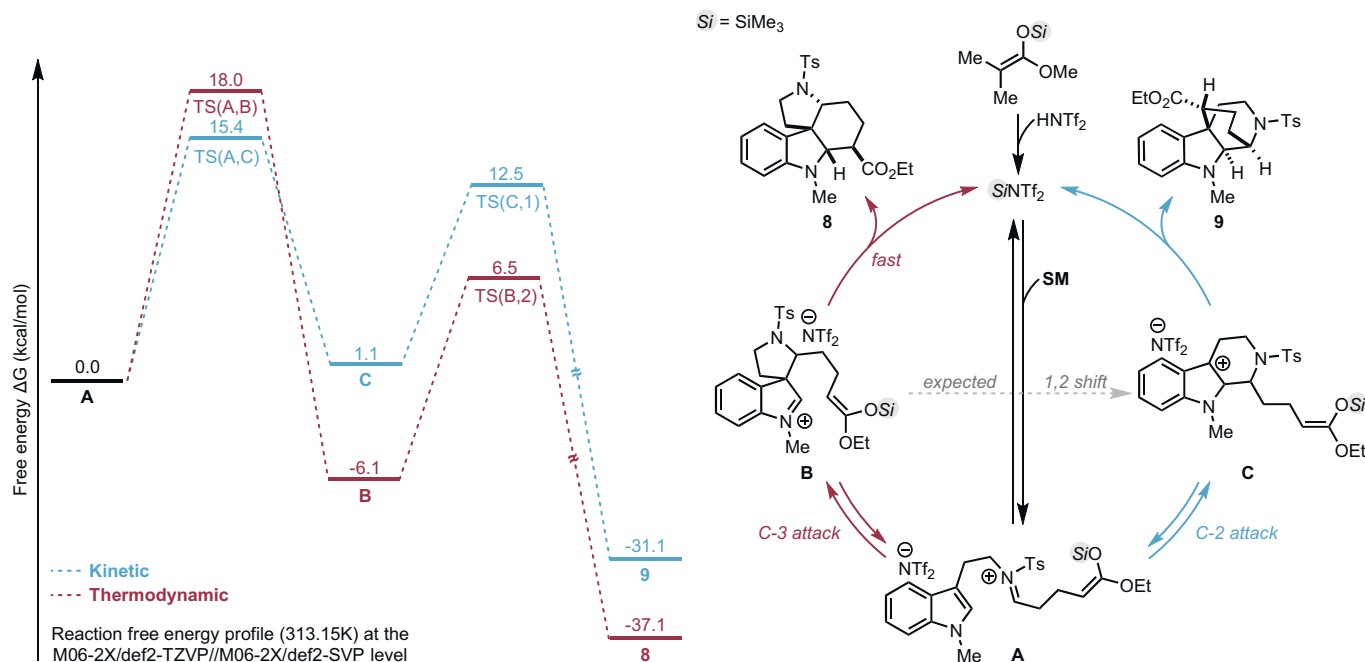
core structure typical of akuamma alkaloids. In addition, the formal total synthesis of 11-demethoxy-epi-myrtoidine **10** was realized.[7] Moreover, isomer **9** could hypothetically serve as an intermediate for the synthesis of (±)-akuammiline **11**.

3.3 *Mechanistic Insights*

To better understand the switch of selectivity observed during the *intra*-molecular annulation, we turned to DFT calculations. We used a computational pipeline[8] that utilizes the graph-based Molassembler library[9] in which multiple conformers of each intermediate and transition state were computed at the M06-2X[10]/def2-TZVP[11]//M06-2X/def2-SVP level (Scheme 6). After preformation of the active silyl bistriflimide catalyst, the ring opening of the cyclobutane provided compound **A** bearing a Z silyl enol ether, which served as the starting point of the calculations. An exothermic C(3) attack from the indole moiety onto the iminium led to **B**. On the other hand, we were surprised to identify that the direct C(2) attack of the indole onto the iminium, leading to intermediate **C**, exhibited an even lower energy barrier and was therefore favored under kinetic conditions. Interestingly, the anticipated Ciamician-Plancher rearrangement[12] (1,2 shift) from **B** to **C** could not be located. Finally, in both cases Mannich reaction allowed the closing of the rings irreversibly to give the two final products **8** and **9**. The computed energy profiles matched the experimental observations. At lower temperatures, we observed a high selectivity for the kinetic product **9**, driven by the faster C(2) attack to intermediate **C** and its low energy barrier for cyclization. Conversely, as the temperature rises, the route to the more stable intermediate **B** becomes accessible, leading to product **8**. However, the selectivity diminishes in this scenario, likely due to the low energy barrier for both cyclization steps, allowing the formation of the kinetic product **9** *via* intermediate **C** to occur.

4. Conclusions

DA strained mono-acceptor rings serve as strategic building blocks due to their versatile reactivity. We discovered that silylium catalysts effectively activate these less-reactive strained rings. This enables their utilization in dearomative [3+2] and [4+2] annulation reactions with indoles, resulting in the generation of valuable alkaloid-based scaffolds. Additionally, we anticipate that the de-

Scheme 5. Divergent intra-molecular [4+2] annulation of amino cyclobutane **7** containing an indole moiety.

Scheme 6. Free energy profile for the intra-molecular reaction and associated mechanism.

velopment of new methods to access donor-acceptor cyclobutane rings will pave the way for further advancements in this field.

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